REMARKS

Claims 1, 3, 4 and 9-14 are pending in this application. Claims 11-14 have been withdrawn from consideration. By this Amendment, claims 1 and 10 are amended to define the presently claimed subject matter. Support for the amendment to claims 1 and 10 can be found, for example, in the present specification at page 6, lines 1-15. Withdrawn claims 11-14 are amended for consistency. No new matter is added by this Amendment.

Entry of the amendments is proper under 37 CFR §1.116 because the amendments: (a) place the application in condition for allowance (for the reasons discussed herein); (b) do not raise any new issue requiring further search and/or consideration (as the amendments amplify issues previously discussed throughout prosecution); (c) do not present any additional claims without canceling a corresponding number of finally rejected claims; and (d) place the application in better form for appeal, should an appeal be necessary. The amendments are necessary and were not earlier presented because they are made in response to arguments raised in the final rejection. Entry of the amendments is thus respectfully requested.

I. Rejection Under 35 U.S.C. §103(a)

Claims 1, 3, 4, 9 and 10 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Van Rossum, et al., Review Article: Glycyrrhizin As A Potential Treatment For Chronic Hepatitis C, Aliment Pharmacol. Theor., Vol. 12, pages 199-205 (1998) ("Van Rossum") in view of U.S. Patent Application Publication No. 2002/0147201 ("Chen").

The Patent Office alleges that Van Rossum discloses administering a glycyrrhizin solution referred to as Stronger Neo Minophagen C ("SNMC") to patients. See Van Rossum, page 203, column 1, Clinical Investigations, first paragraph. However, the Patent Office admits that Van Rossum fails to disclose the glycyrrhizin, cysteine and aminoacetic acid concentrations and the absence of sulfite recited in claims 1 and 10. See Office Action, page

5, lines 14-19. The Patent Office thus introduces Chen as allegedly remedying the deficiencies of Van Rossum.

Applicants submit that the cited references do not describe all of the limitations of amended independent claims 1 and 10. Specifically, the cited references do not teach or suggest at least the recited constituents at the recited concentrations, wherein no sulfites are contained, and wherein the glycyrrhizin, cysteine and aminoacetic acid are dissolved in water.

A. No Reason Or Rationale To Combine Van Rossum With Chen

Van Rossum does not describe that the glycyrrhizin, cysteine and aminoacetic acid are dissolved in water, as recited in claims 1 and 10. Van Rossum instead describes that the glycyrrhizin, cysteine and aminoacetic acid are dissolved in a physiological saline solution. See Van Rossum, page 203, right column, lines 27-30 of the present specification. Thus, the solvent used to dissolve the effective ingredients of Van Rossum and the effective ingredients in claims 1 and 10 are entirely different.

Furthermore, as compared to being dissolved in water, the osmotic pressure ratio of Van Rossum's composition (SNMC) increases by about 1. The higher the osmotic pressure ratio of a drug, the more severely the drug results in an injurious effect to tissue. A pharmaceutical composition having higher osmotic pressure is thus not preferable for injection.

Furthermore, as admitted by the Patent Office, Chen does not describe a composition comprised of glycyrrhizin, cysteine and aminoacetic acid or a composition at the recited concentrations. Nonetheless, the Patent Office alleges that because (1) Chen describes an concentration of glycyrrhizin that is greater than the concentration of glycyrrhizin described in Van Rossum and (2) Van Rossum allegedly describes that aminoacetic acid (glycine) and cysteine play a physiological role, it would allegedly have been obvious to one having

ordinary skill in the art to have increased the concentration of cysteine and aminoacetic acid proportionately with the glycyrrhizin. See Office Action, page 5.

The Patent Office's allegations are not supported by the disclosure of either Van Rossum or Chen and are thus clearly based on impermissible hindsight. Van Rossum merely describes that cysteine should be detoxificative through cysteine conjugation in the liver and aminoacetic acid (i.e., glycine) is added to prevent pseudoaldosteronism. See Van Rossum, page 203, left column. In other words, Van Rossum merely describes the characteristics of cysteine and aminoacetic acid and does not describe that the physiological roles even occur when complexed with glycyrrhizin. Van Rossum thus does not provide any reason or rationale to have increased the concentration of cysteine and aminoacetic acid if the concentration of glycyrrhizin in also increased. For this reason, the Patent Office's allegation is based on impermissible hindsight and unsupported by the disclosure of Van Rossum. Furthermore, even if cysteine and aminoacetic acid both have physiological roles, this would not have led one having ordinary skill in the art to have increased the concentration of cysteine and aminoacetic acid in lock step as the Patent Office theorizes.

Chen at best merely describes increasing the concentration of glycyrrhizin complexed with an active agent, not glycyrrhizin as a pharmaceutical agent in its own right. For this reason, Chen specifically defines "active agent" differently than "glycyrrhizin." See Chen, paragraphs [0021], [0031] and [0049]. As such, the glycyrrhizin referred to in Chen has no intended pharmacological use as Chen specifies that the active agent (i.e., famotidine) reverse complexes from the glycyrrhizin at a low pH and thus eventually forms a protonated active ingredient that more easily dissociates in the stomach. See Chen, paragraph [0053]. Chen thus describes a composition having glycyrrhizin as an additive to enhance delivery of other pharmaceuticals.

Thus, Chen would have merely provided one having ordinary skill in the art would with a reason or rationale to have increased the concentration of a different glycyrrhizin compound (i.e., glycyrrhizin complexed with an active agent) and not glycyrrhizin as a pharmaceutical agent in its own right.

Furthermore, as discussed above, Van Rossum describes that the glycyrrhizin, cysteine and aminoacetic acid are dissolved in a physiological saline solution, while the present claims recite dissolving glycyrrhizin, cysteine and aminoacetic acid in water. Thus, the solvent used to dissolve the effective ingredients of Van Rossum is entirely different from the solvent used to dissolve the effective ingredients in claims 1 and 10. Thus, Van Rossum would not have provided one ordinary skill in the art with any reason or rationale to have attempted to increase the concentration of glycyrrhizin, cysteine and aminoacetic acid in an entirely different solvent from that of Van Rossum.

As such, Chen would not have provided one of ordinary skill in the art with any reason or rationale to have altered the SNMC solution of Van Rossum to (1) increase the concentration of all the active ingredients, and (2) exclude sulfite, with any reasonable expectation of success.

B. Unpredictability Regarding No Sulfite

Applicants respectfully submit that the cited references do not describe a pharmaceutical composition comprising glycyrrhizin, cysteine and aminoacetic acid, wherein substantially no sulfite is contained.

In the Amendment filed January 4, 2010, Applicants argued that Chen would not have provided one of ordinary skill in the art with a reason or rationale to have attempted to eliminate the sulfite from the SNMC of Van Rossum because Chen discloses that sulfites are perfectly acceptable additives in the composition described therein.

The Patent Office disagreed and cited MPEP 2142.02 III, which recites:

> "[A] patentable invention may lie in the discovery of the source of a problem even though the remedy may be obvious once the source of the problem is identified. This is part of the 'subject matter as a whole' which should always be considered in determining the obviousness of an invention under 35 U.S.C. § 103." *In re Sponnoble*, 405 F.2d 578, 585, 160 USPQ 237, 243 (CCPA 1969). However, "discovery of the cause of a problem . . does not always result in a patentable invention. . . . [A] different situation exists where the solution is obvious from prior art which contains the same solution for a similar problem." *In re Wiseman*, 596 F.2d 1019, 1022, 201 USPQ 658, 661 (CCPA 1979) (emphasis in original).

The Patent Office further cited Mollica as allegedly evidencing the level of ordinary skill in the art for its teaching that the choice of excipients, such as sulfites, allegedly affects the stability of a pharmaceutical formulation.

Applicants respectfully submit that Mollica nowhere describes that sulfites cause precipitation *of glycyrrhizin, cysteine or aminoacetic acid.* On the contrary, Mollica both describes that bisulfite can cause precipitation (p. 449, left column, lines 2-3) and that sulfite can cause increased stability (Table V, "epinephrine").

Therefore, the evidence (Mollica) indicates that there is a high degree of uncertainty in the art as to the performance of a given type of additive with different compounds in view of the reactions that may occur. See Mollica, page 44, bottom right column. Van Rossum indicates the successful use of a sulfite in a composition of glycyrrhizin, cysteine and aminoacetic acid at low concentrations. Thus, one having ordinary skill in the art, in viewing Van Rossum, would have continued to use sulfite as it was thought to be successfully used with compositions of glycyrrhizin, cysteine and aminoacetic acid. A person having ordinary skill in the art would not have been led by Chen or Mollica to replace the sulfite of Van Rossum with any reasonable expectation of success, in view of the unpredictability associated with the sulfite additive. Thus, the elimination of sulfites in Van Rossum would not have been obvious.

C. **Unexpected Results Regarding No Sulfite**

Van Rossum, alone or in combination with Chen, does not describe that a pharmaceutical composition comprised of glycyrrhizin, cysteine and aminoacetic acid in the recited concentration and including substantially no sulfite unexpectedly results in a pharmaceutical composition with improved stability and no glycyrrhizin precipitates.

As described in the present specification, two sets of experiments (Example 1 and Example 2) were prepared to determine the influence of sulfite on a pharmaceutical composition comprised of glycyrrhizin, cysteine and aminoacetic acid. The details for the preparation of the solutions of Example 1 and Example are described at pages 6-8 of the present specification.

As shown below in Tables 1 and 2 (and Tables 1 and 2 of the original specification), the greater the concentration of sodium sulfite, the more the amount of cysteine is reduced as time passes. Furthermore, adding sodium sulfite precipitates the glycyrrhizin. However, in the cases where no sodium sulfite was added, glycyrrhizin did not precipitate and the amount of cysteine was not significantly reduced, which thus results in an improved stability of the pharmaceutical composition.

Table 1

			Adding amount of sodium sulfite (mg/mL)		
			Solution 1	Comp. Solution 1	Comp. Solution 2
			0	2.4	4.0
pH at manufacturing			7.22	7.49	7.29
Presence or absence of precipitation of glycyrrhizin	After 4 years at 25°C		-	+	+
Amount of cysteine hydrochloride(%)	Before sterilization		97.3	101.6	98.9
	After sterilization		94.4	95.2	91.1
	60 °C	After 3 days	89.7	87.8	81.4
		After 7 days	81.2	71.3	64.2
		After 14 days	77.8	66.5	53.9
	40 °C	After 2 months	89.4	86.0	70.3
		After 4 months	83.6	77.7	68.5

Table 2

	Concentration of cysteine hydrochloride (mg/mL)		8	6	4
Solution 2 (Non-addition of Sulfite)	Amount of cysteine hydrochloride (%)	Initial	100.0	100.0	100.0
		4 days	93.5	97.5	94.3
		7 days	88.6	94.5	89.5
		14 days	82.8	82.4	88.7
Comp. Solution 3 (Addition of Sulfite)	Amount of cysteine hydrochloride (%)	Initial	100.0	100.0	100.0
		4 days	73.6	84.4	88.8
		7 days	53.1	70.4	77.1
		14 days	40.4	52.2	59.8

In view of the above evidence, Applicants respectfully submit that the absence of sulfites unexpectedly results in a pharmaceutical composition with improved stability and no glycyrrhizin precipitates.

Furthermore, page 2 of the present specification describes that sulfites are conventionally added to compositions comprising glycyrrhizin, cysteine and aminoacetic acid in order to increase stability, i.e. decrease precipitation and degradation. In this way, a person of ordinary skill in the art would not have expected to increase stability by lessening the amount of a stabilizer, much less by omitting it altogether.

Therefore, the Applicants have demonstrated highly unexpected results by showing that stability can be increased by not including a compound that was known and conventionally used to increase stability.

II. Rejoinder

Applicants respectfully submit that claims 1, 3, 4, 9 and 10 are in a condition for allowance for at least the reasons discussed above, and therefore Applicants respectfully submit that rejoinder and consideration of withdrawn claims 11-14 is proper. MPEP §821.04 states that claims eligible for rejoinder must depend from or require all the limitations of an allowable claim. Applicants suggest that claims 11-14, drawn to methods of treating hepatic diseases or methods of treating allergy require all the limitations of independent claim 1, and therefore are eligible for rejoinder under MPEP §821.04. Accordingly, rejoinder of claims 11-14 is respectfully requested.

III. Conclusion

In view of the foregoing, it is respectfully submitted that this application is in condition for allowance. Favorable reconsideration and prompt allowance of claims 1, 3, 4 and 9-14 are earnestly solicited.

Should the Examiner believe that anything further would be desirable in order to place this application in even better condition for allowance, the Examiner is invited to contact the undersigned at the telephone number set forth below.

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